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Gut microbiome modulation through non-pharmacological therapy in psychiatric disorders: neurotransmitter synthesis, neuroplasticity, and brain-gut signaling

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ABSTRACT

Psychiatric disorders affect over 970 million people globally, with substantial personal, social, and economic costs that continue to rise despite advances in treatment. Current pharmacological approaches show limited efficacy for many patients, with significant side effects and high discontinuation rates. The integration of microbiome science with psychiatric research may offer new perspectives on disease etiology, biomarker development, and therapeutic intervention. Recent advances in microbiome research reveal that the gut microbiome directly synthesizes neurotransmitters and their precursors, while microbial metabolites produced by the microorganisms through their metabolic activities, cross the blood-brain barrier (BBB) to influence regulate microglial activation, synaptic plasticity, neurogenesis, and neural circuit development associated with our brain's function. Specific gut bacterial taxa may demonstrate causal relationships with psychiatric symptoms through vagal, immune, and metabolic pathways. Gut dysbiosis patterns consistently emerge across major psychiatric conditions associated with distinct microbial signatures. Scientific research has discovered that disrupted circadian rhythm and dysregulated stress response system especially the hypothalamic pituitary adrenal (HPA) axis both disrupt gut microbiota composition and function, leading to health issues like metabolic syndrome, gastrointestinal disorders, and mental wellness issues. Understanding these mechanisms may open unprecedented opportunities for non-pharmacological approaches that integrate microbiome analysis and targeted interventions. The authors of this article aim to explore how non-pharmacological intervention methods such as mental wellness behavioral therapy and educational therapy can be integrated with gut microbiome knowledge to enhance patient outcomes, focusing on mental health, gastrointestinal, and metabolic disorders.

Keywords: Educational therapy, mental wellness behavioral therapy, gut-brain axis, microbial metabolites, neurotransmitter synthesis, neuroplasticity

INTRODUCTION

The human gut refers to the gastrointestinal tract, which runs from our mouth through the esophagus, stomach, small intestine, large intestine (colon), rectum and anus. This gut which contains over 100 trillion of microorganisms (or gut microbiota) made up of over 1,000 bacterial species (bacteria, archaea, fungi, viruses, protozoa and helminths) is referred to as gut microbiome. The gut microbiome is responsible for many different bodily functions such as breaking down food to ensure that its nutrients are absorbed and waste materials taken out of the body. It is also responsible for immunity and general well-being of the individual.[1] The gut microbiome has emerged as a critical modulator of brain function and mental health.[2] This intricate ecosystem influences psychiatric disorders through direct effects on neurotransmitter synthesis, neuroplasticity mechanisms, and interactions with host genetic factors that determine individual vulnerability to mental illness.[3]

The gut microbiome represents a dynamic environmental factor that influence neurodevelopment, stress response systems, and neurotransmitter pathways critical for mental health.[4] The neurobiological mechanisms underlying gut-brain communication involve multiple interconnected pathways that directly impact neurotransmitter synthesis and neural plasticity. Gut bacteria produce gamma-aminobutyric acid (GABA), serotonin, dopamine, and other neuroactive compounds, while microbial metabolites including short-chain fatty acids (SCFAs) cross the blood-brain barrier (BBB) to influence synaptic function, neurogenesis, and neural circuit development.[5]

Association of the Gut-Brain Axis and Enteric Nervous System

The gut microbiome communicates bidirectional with the central nervous system (CNS) through multiple mechanisms including the vagus nerve, immune system modulation, neurotransmitter production, metabolite synthesis, and epigenetic regulation.[6] This bidirectional communication known as gut-brain axis is not restricted only to vagus nerve, albeit the vagus nerve serves as the primary channel connecting the gut and brain (see Figure 1),[7] transmitting bidirectional signals that influence both the peripheral nervous system (PNS) and CNS functions.[8] Bacterial metabolites and neurotransmitters activate vagal afferent neurons in the enteric nervous system, which transmit signals to the brainstem and subsequently modulate central neurotransmitter synthesis and release. Vagotomy studies have demonstrated that severing this nerve abolishes many microbiome-induced behavioral and neurochemical changes.[8]

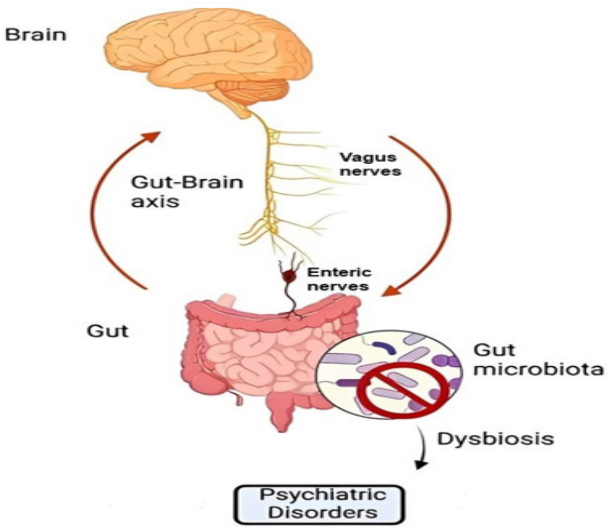

Figure 1. Bidirectional communication of the gut-brain axis

Interestingly, as estimated in the studies by Magalhães and Castelucci,[9] there are some 500 million enteric neurons embedded on the walls of the gut. These enteric neurons range from motor neurons, sensory neurons, interneurons, vasodilator neurons to secretomotor neurons. The vast network of these neurons covering from the esophagus to anus is known as the enteric nervous system (ENS). The ENS functions autonomously like another "brain" in regulating our digestive processes (which include motility). However, this "second brain" also maintains extensive bidirectional communication with our CNS.[10]

GUT BACTERIA

Gut bacteria produce a variety of compounds, including microbial metabolites, neurotransmitter precursors, neurotransmitters (serotonin, GABA and dopamine) and engage in other processes that signal the brain through neural, hormonal, and immune pathways. The enteric neurons in the gut respond directly to bacterial metabolites and neurotransmitters, with specific bacterial strains capable of activating or inhibiting enteric neural circuits[11] (see Table 1).[5,12-14] This local neural processing significantly influences gut-brain axis' ascending signals to the brain and descending autonomic control of gut function.[14] The vagus nerve transmits bacterial signals to the brain, influencing neurotransmitter release and mood (a direct communication line). Vagal afferent neurons also express receptors for microbial metabolites, bacterial lipopolysaccharides, and gut hormones, allowing direct sensing of microbiome composition and activity.

Gut dysbiosis (alteration to the microbiome resulting in an imbalance in the microbiota) leading to the production of inflammatory molecules and increased permeability of the intestinal barrier, disrupts enteric neural function, affecting gastrointestinal motility, barrier function, and neurotransmitter production in ways that reverberate throughout the nervous system to influence psychiatric symptoms[14] (see Figure 2).[12] Gut dysbiosis may leads to

Table 1. Influence of gut bacteria on the brain

Mechanism	Description	Key processes
Direct neurotransmitter production	Gut bacteria synthesize neurotransmitters like serotonin, GABA, dopamine, and norepinephrine.	Gut bacteria produce neurotransmitters that signal the brain indirectly through blood circulation or the vagus nerve (a direct gut-brain connection).
Production of neurotransmitter precursors	Gut bacteria generate precursors (e.g., tryptophan, glutamate) used by the host to synthesize neurotransmitters.	Gut bacteria supply precursors that the host uses to synthesize neurotransmitters, modulating brain chemistry (like providing ingredients for the brain's 'recipes').
Modulation of host neurotransmitter synthesis	Bacterial metabolites influence host cells to produce neurotransmitters.	Bacterial metabolites, especially SCFAs, stimulate host neurotransmitter production and can directly affect the brain (SCFAs as messengers boosting brain chemicals).
Immune system modulation	Gut bacteria interact with the immune system, indirectly affecting brain neurotransmitter levels and function.	Gut bacteria interact with the immune system; dysbiosis can trigger inflammation that affects brain function (inflammation as a false alarm).
Blood-brain barrier (BBB) integrity	Gut bacteria maintain BBB integrity, regulating what enters the brain.	Gut bacteria produce SCFAs that maintain the BBB, protecting the brain from harmful substances (reinforcing the brain's security wall).
Hormonal regulation	Gut bacteria influence hormone production, which can affect brain signaling and neurotransmitter activity.	Gut bacteria modulate hormones like cortisol and oxytocin, which influence brain signaling (adjusting the body's 'mood playlist').
Metabolic by-products	Bacterial metabolites, beyond SCFAs, influence brain function.	Bacterial metabolites modulate neurotransmitter pathways in the brain (fine-tuning brain chemistry).

GABA: Gamma-aminobutyric acid, SCFAs: Short-chain fatty acids serotonin deficits and reduced levels of GABA, disrupting brain connectivity and functionality, affecting mood and behavior.[15,16]

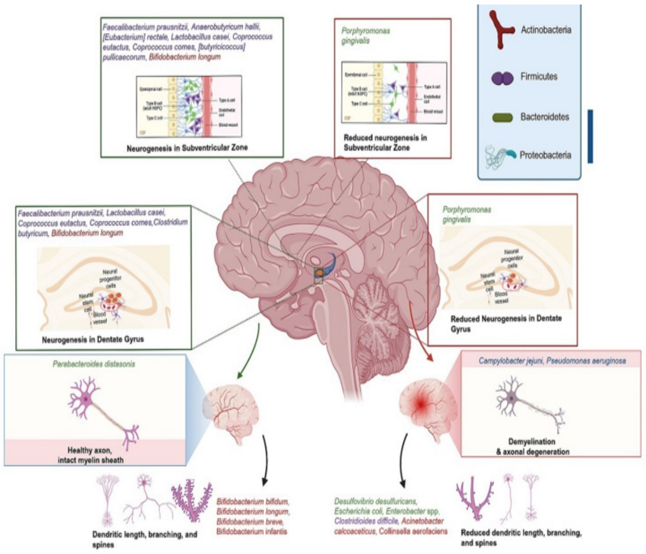

Figure 2. Gut bacteria in association with our brain & neuroplasticity functions

Table 2[13,15,17-51] shows a comprehensive list of known contributions of gut bacteria to gut-brain axis communication associated with the brain neuroplasticity and different psychiatric disorders such autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BD), attention deficit-hyperactive disorder (ADHD), anxiety disorder, post-acute COVID symptoms (PACS), Alzheimer's disease (AD), Parkinson disease (PD) and schizophrenia spectrum disorder (SSD).

MICROBIAL METABOLITES AND SIGNALING

According to Zuffa et al.,[52] when food is processed by our digestive enzymes, the gut bacteria transform this food into hundreds of different microbial metabolites through fermentation and other metabolic processes (see Table 3).[20,53-60] These microbial metabolites enter the bloodstream and travel throughout the body, acting as molecular messengers that influence virtually every organ system such as immune function, metabolism, cardiovascular health, brain function and mood. The gut microbiome is increasingly recognized not just as a digestive aid, but as a crucial "organ" that produces hundreds of bioactive compounds essential for optimal health. The specific mix of metabolites the microbiome produces depends on factors like diet, lifestyle, genetics, medications, and the particular species of microbes the gut is harboring, making every metabolite profile uniquely related to every identity.

Short-Chain Fatty Acids (SCFAs)

In the studies conducted by Yassin and his colleagues,[12] the SCFAs are the most abundant and well-studied metabolites that promote BBB integrity. Particularly the acetate, propionate and butyrate, they represent critical signalling

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders

Microorganism/process	Associated psychiatric disorders	Role in brain neuroplasticity	Key findings
Acinetobacter calcoaceticus	No direct association	May contribute to inflammation, potentially affecting neuronal health	Part of gut microbiota, lower virulence, potential pro-inflammatory effects
Actinobacteria	ASD, potentially MDD, BD, SSD	May support gut barrier function, reducing inflammation	Higher in ASD, linked to GI symptoms and behavior
Actinomyces naeslundii	PACS (anxiety, depression)	Not directly studied	Higher in PACS, linked to psychological issues
Akkermansia muciniphila	ASD, MDD	Supports gut barrier integrity, aiding neuronal health	Lower in ASD and MDD, associated with metabolic health
Alistipes	MDD	May influence inflammation and neurotransmitter signaling	Increased in MDD, linked to systemic inflammation
Anaerobutyricum hallii	Anxiety, PTSD	Produces butyrate, supports synaptic plasticity and reduces neuroinflammation	Butyrate producer, linked to reduced inflammation in PTSD, potential biotherapeutic
Bacillus spp.	MDD, anxiety, Parkinson's disease	Supports synaptic plasticity through neurotransmitter production (dopamine, serotonin)	Synthesizes dopamine and other neurotransmitters, acts as probiotics to improve mood, influences gut-brain axis through secretome
Bacillus subtilis	Aggression, MDD, anxiety, Parkinson's disease	Supports synaptic plasticity through serotonin and tryptophan production	Probiotic that prevents aggression, supports serotonin synthesis, reduces neuroinflammation, potential benefits in Parkinson's disease
Bacillus mycoides	Potentially SSD, MDD, addiction	Supports synaptic plasticity through dopamine production	Synthesizes dopamine, a neurotransmitter critical for brain function and behavior
Bacteroides	ASD, ADHD, MDD, addiction (CNS stimulants)	Produces neurotransmitters and SCFAs, supports synaptic plasticity	Mixed results in ASD, increased in ADHD and PACS
Bacteroides fragilis	Depression, ASD, Alzheimer's, multiple sclerosis	May support or disrupt synaptic plasticity via immunomodulation and metabolic signaling	Produces polysaccharide A (PSA) with immunomodulatory effects, modulates depression-like behavior, linked to Alzheimer's and ASD
Bacteriophages	ASD	May modulate bacterial populations affecting brain function	Altered in ASD, influencing microbial dynamics
Bifidobacterium	ASD, ADHD, MDD, BD, SSD, addiction (alcohol)	Produces GABA, supports synaptic plasticity	Lower in ASD, higher in ADHD, supports neural signaling

The table continues

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders (The table continues)

Bifidobacterium spp.	Depression, anxiety, ASD, stress-related disorders	Supports synaptic plasticity through neurotransmitter production and anti-inflammatory effects	Key players in gut-brain axis, influence mental health via neurotransmitter production, immune modulation, stress response regulation
Bifidobacterium longum	MDD, anxiety, PACS	Produces GABA and SCFAs, enhances synaptic plasticity and reduces stress	Supplementation reduces depressive symptoms; lower in PACS
Blautia	ASD, ADHD	Produces SCFAs, supports anti-inflammatory pathways	Lower in ASD, increased in ADHD
Butyricicoccus pullicaecorum	Anxiety	Produces butyrate, potentially supports synaptic plasticity	Decreased in anxiety, linked to reduced anti-inflammatory effects
Campylobacter jejuni	Anxiety	May disrupt neural signaling	Induces anxiety-like behavior in rodents
Candida	ASD, ADHD	May contribute to inflammation	Higher in ASD, linked to GI symptoms
Clostridium	ASD, MDD, BD, PASC	Produces neurotransmitter precursors (tryptophan), SCFAs, and secondary bile acids via 7α-dehydroxylation; some species produce neurotoxins	Higher in ASD, linked to GI and behavioral symptoms; contributes to mood regulation via tryptophan metabolism
Clostridium spp.	Depression, anxiety, Parkinson's, multiple sclerosis	Can support or disrupt synaptic plasticity through neurotransmitter modulation and immune signaling	Influences gut-brain axis, some species linked to neurological disorders, others maintain gut homeostasis
Clostridium butyricum	MDD, anxiety	Produces butyrate, supports synaptic plasticity and reduces stress	Supplementation reduces depressive symptoms; enhances gut-brain signaling
Clostridioides difficile	ASD, Alzheimer's, Parkinson's, multiple sclerosis	May disrupt gut-brain axis, negatively affecting neuroplasticity	Linked to neurological disorders via toxins and inflammation
Collinsella	ASD	Associated with pro-inflammatory states	Higher in ASD, linked to inflammation
Collinsella aerofaciens	ASD	May contribute to inflammation, potentially affecting neuroplasticity	Higher in ASD, associated with pro-inflammatory states
Coprococcus	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, anti-inflammatory
Coprococcus comes	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, linked to anti-inflammatory effects
Coprococcus eutactus	ASD, MDD	Produces butyrate, supports neuronal health	Lower in ASD and depression, linked to anti-inflammatory effects
Coriobacteriaceae	BD	Linked to metabolic and inflammatory pathways	Increased in BD, associated with cholesterol metabolism
Corynebacterium glutamicum	Potentially SSD, MDD, anxiety	Produces glutamate, supporting GABA synthesis and synaptic plasticity	Produces L-glutamate via mechanosensitive channels, influences gut-brain axis
Desulfovibrio	ASD	Produces hydrogen sulfide, linked to GI issues	Mixed results in ASD, associated with gut symptoms
Desulfovibrio desulfuricans	ASD	Produces hydrogen sulfide, potentially disrupting neural signaling	Mixed results in ASD, linked to gut dysbiosis
Dialister	ASD, ADHD	Supports gut health, may influence neural signaling	Lower in ASD and unmedicated ADHD
Eggerthella	MDD, BD, SSD	Linked to symptom severity via inflammation	Higher in MDD, BD, SSD
Enterobacteriaceae	ASD	Includes pathogens, may increase inflammation	Mixed results in ASD, linked to gut dysbiosis
Enterobacter spp.	ASD, potentially MDD, BD, SSD	May influence neurotransmitter production and inflammation	Altered in psychiatric disorders, linked to gut-brain axis
Enterococcus	Addiction (alcohol), potentially MDD	Produces neurotransmitters like dopamine, influences inflammation	Increased in alcoholics, may exacerbate inflammation and mood dysregulation
Escherichia coli	ASD, MDD, potentially anxiety	Produces dopamine, serotonin precursors (tryptophan), and indoles, modulating mood and cognition	Supplies tryptophan for serotonin synthesis; dopamine production affects reward systems
Escherichia coli K-12	Potentially Parkinson's, neuroinflammation-related disorders	May disrupt synaptic plasticity through neuroinflammation and barrier disruption	Model organism, influences gut-brain axis via intestinal barrier effects and potential neuroinflammation
Eubacterium rectale	PTSD	Produces butyrate, potentially supports synaptic plasticity	Part of Lachnospiraceae, associated with reduced inflammation in PTSD
Faecalibacterium	ASD, MDD, BD, SSD, ADHD, PACS	Produces butyrate, supports anti-inflammatory pathways and neuroplasticity	Lower in multiple disorders, protective against inflammation
Faecalibacterium prausnitzii	ASD, MDD, BD, SSD, ADHD, PACS	Produces butyrate, enhances synaptic plasticity and reduces neuroinflammation	Lower in multiple disorders, key anti-inflammatory bacterium
Firmicutes	ASD, ADHD, MDD, BD, addiction	Imbalance affects gut barrier and neurotransmitter production	Mixed results, linked to gut-brain axis

The table continues

Table 2. Roles of gut bacteria in neuroplasticity associated with psychiatric disorders (The table continues)

Fusobacteria	ASD	Linked to gut dysbiosis	Increased in ASD, affects volatile organic compounds
Hafnia alvei	Potentially binge eating disorder, obesity-related depression	May influence synaptic plasticity through appetite regulation	Probiotic reducing food intake via ClpB protein mimicking alpha-MSH, influences gut-brain axis
Klebsiella	ASD	Potential pathogen, may increase inflammation	Mixed results in ASD
Klebsiella pneumoniae	Depression, anxiety, Alzheimer's, epilepsy	May disrupt synaptic plasticity through neuroinflammation and infection	Causes infections affecting brain, exacerbates neurological disorders like Alzheimer's and epilepsy
Lactobacillus	ASD, MDD, BD, SSD, anxiety	Produces GABA and serotonin, supports synaptic plasticity	Mixed in ASD, higher in MDD, BD, SSD, reduces OCD-like behaviors
Lactobacillus spp.	MDD, anxiety, ASD, SSD, Alzheimer's	Supports synaptic plasticity through neurotransmitter production and anti-inflammatory effects	Probiotics modulating gut-brain axis, therapeutic potential in psychiatric and neurological disorders
Lactobacillus casei	MDD, anxiety	Produces GABA, reduces stress and enhances neuroplasticity	Supplementation reduces depressive symptoms; modulates vagus nerve signaling
Lactobacillus helveticus	MDD, anxiety	Produces GABA, reduces stress and enhances neuroplasticity	Supplementation alleviates depressive symptoms; modulates vagus nerve signaling
Lactobacillus rhamnosus	MDD, anxiety, ASD	Produces GABA, enhances synaptic plasticity and reduces stress	Supplementation reduces anxiety and depressive symptoms, improves ASD behaviors in animal models
Lactiplantibacillus plantarum	ASD, MDD, anxiety	Produces serotonin, supports mood regulation and synaptic plasticity	Enhances serotonin production, reducing anxiety and depressive symptoms
Lactococcus lactis	Anxiety, depression	May support synaptic plasticity and brain development	Probiotic modulating gut-brain axis, reduces anxiety-like behavior in preclinical studies
Methanobrevibacter	ASD	Affects gut transit time via hydrogen metabolism	Mixed results in ASD
Oscillibacter	MDD	Linked to systemic inflammation	Increased in MDD
Parabacteroides	ASD	Associated with GI issues	Mixed results in ASD
Parabacteroides distasonis	ASD, MDD	Produces GABA, supports gut-brain axis and synaptic plasticity	Lower in ASD, induces depressive-like behavior in Crohn's disease models
Peptostreptococcaceae	ADHD	Produces GABA, may alter neural signaling	Increased in ADHD, linked to inattention
Phascolarctobacterium	ASD	Reduced SCFAs, linked to GI issues	Mixed results in ASD
Porphyromonas gingivalis	Alzheimer's disease (with psychiatric symptoms)	May contribute to neurodegeneration, negatively affecting neuroplasticity	Associated with Alzheimer's through neuroinflammation
Prevotella	ASD	Breaks down carbohydrates, linked to diet	Lower in ASD, associated with GI symptoms
Proteobacteria	ASD, MDD	Includes pathogens, linked to inflammation	Higher in ASD, associated with dysbiosis
Proteus vulgaris	Potentially Parkinson's, SSD, MDD, addiction	May influence synaptic plasticity through dopamine production	Synthesizes dopamine, part of gut microbiota, potentially influences gut-brain axis
Pseudomonas aeruginosa	Meningitis	Induces memory impairment, increases pro-inflammatory response, alters brain histoarchitecture	Opportunistic pathogen, potential indirect effects through infections
Roseburia	ASD	Produces butyrate, reduces inflammation	Lower in ASD, supports gut health
Ruminococcus	ASD, PACS	Involved in carbohydrate breakdown	Mixed in ASD, higher in PACS
Ruminococcaceae_UCG_004	ADHD	Linked to inattention symptoms	Increased in ADHD
Serratia spp.	Potentially SSD, MDD, addiction	May influence synaptic plasticity through dopamine production	Synthesizes dopamine, part of gut microbiota, potentially influences gut-brain axis
Streptococcus	MDD, BD, SSD	Linked to symptom severity via inflammation	Higher in MDD, BD, SSD
Sutterella	ASD	Associated with GI inflammation	Higher in ASD
Tannerella spp.	No direct association	Unknown	Limited evidence, primarily oral bacteria, potential indirect effects via inflammation
Veillonella	ASD	May contribute to gut dysbiosis	Higher in ASD
Verrucomicrobia	ASD, addiction (CNS stimulants)	Linked to gut dysbiosis	Increased in ASD and addiction
7α-dehydroxylation	Potentially MDD, BD, PACS	Converts primary bile acids to secondary bile acids, influencing gut-brain signaling via bile acid receptors	Secondary bile acids modulate neuroinflammation and mood; altered in PACS

GABA: Gamma-aminobutyric acid, SCFAs: Short-chain fatty acids, ASD: Autism spectrum disorder, MDD: Major depressive disorder, BD: Bipolar disorder, ADHD: Attention deficit-hyperactive disorder, PACS: Anxiety disorder, post-acute COVID symptoms, AD: Alzheimer's disease, PD: Parkinson disease, SSD: Schizophrenia spectrum disorder

Table 3. Functions of microbial metabolites in gut-brain axis

Microbial metabolites	Key components	Functions in gut-brain axis
Short-chain fatty acids (SCFAs)	Acetate, propionate, butyrate, isobutyrate, isovalerate, valerate, formate, caproate	Support energy production, reduce brain inflammation, enhance memory, strengthen BBB.
Neuroactive lipids and bile acids metabolites	Result from bacterial modification of bile acids. Primary (cholic acid, chenodeoxycholic acid), secondary (deoxycholic acid, lithocholic acid, ursodeoxycholic acid, tauroursodeoxycholic acid)	Regulate metabolism, reduce neuroinflammation, protect brain barriers, may improve cognition, though some contribute to cognitive decline.
Tryptophan and indole derivatives	Indole, Indole-3-acetic acid, Indole-3-propionic acid, kynurenic acid, indoxyl sulfate, indole-3-carbinol, indole-3-ethanol, indole-3-pyruvate, indole-3-aldehyde	Modulate brain inflammation, influence mood and behavior, some increase anxiety or oxidative stress.
Polyunsaturated fatty acids (PUFAs) metabolites	Leukotriene B4, Prostaglandin E2, 12-hydroxyheptadecatrienoic acid (from arachidonic acid), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) metabolites	Support brain cell growth, reduce inflammation, aid brain repair, with omega-3 derivatives showing cognitive benefits.
Branched-chain amino acids (BCAAs)	Come from bacterial breakdown of proteins. Leucine, isoleucine, valine	Reduce brain inflammation, support gut barrier health, protect against neurodegenerative diseases.
Nicotinamide (NMN)	Nicotinamide, nicotinic acid, NAD+	Support brain cell energy, reduce inflammation, improve motor function in diseases like ALS.
Trimethylamine N-oxide (TMAO)	TMAO	Linked to increased brain inflammation and cognitive decline, potentially worsening Alzheimer's or Parkinson's.
Phenolic compounds	Created when bacteria process plant polyphenols from foods like berries, tea, and vegetables. Urolithin A, ferulic acid, equol, enterolactone	Provide antioxidant and anti-inflammatory effects, reducing neuroinflammation and protecting brain cells.
Vitamins and cofactors	Vitamin B12, folate, riboflavin, thiamine, biotin	Support energy metabolism and neurotransmitter production, essential for brain health.
Neurotransmitter precursors and neurotransmitters	Tryptophan (serotonin precursor), choline (acetylcholine precursor), tyrosine (dopamine precursor), GABA, dopamine, serotonin	Influence mood, behavior, and cognitive function by supporting neurotransmitter production.
Other metabolites	Lactate, ethanol, polysaccharide A (PSA), endotoxins (LPS)	Lactate boosts brain energy, PSA modulates immunity, LPS may increase brain inflammation.

molecules that cross the BBB and directly influence neural function (see Figure 3).[61] Butyrate demonstrates particularly robust neuroprotective and plasticity-enhancing effects. It increases brain-derived neurotrophic factor (BDNF) expression, promotes dendritic spine formation, enhances long-term potentiation, and supports adult neurogenesis in the hippocampus. BDNF exerts particular importance for depression, anxiety, and cognitive disorders where reduced neurotrophic signaling contributes to synaptic dysfunction and neural atrophy which have direct relevance for mood regulation, learning, memory, and stress resilience.

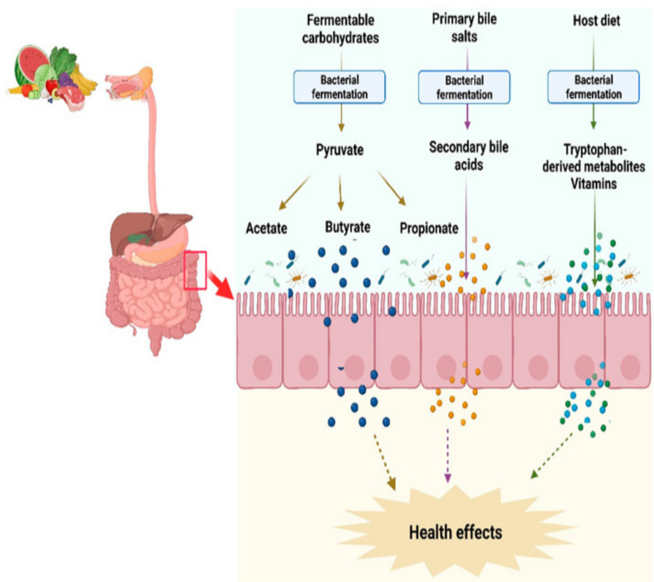

Figure 3. Synthesis of microbial metabolites in the intestine

Propionate influences microglial phenotype that support synaptic plasticity and neuronal survival.[5] This immunomodulatory effect helps explain how gut dysbiosis can lead to neuroinflammation and psychiatric symptoms through altered microglial function. The SCFAs promote oligodendrocyte differentiation and myelin synthesis, while inflammatory conditions can impair myelination and lead to white matter abnormalities. Oligodendrocyte development and myelination processes critical for neural circuit function and cognitive performance.

Neuroactive Lipids and Bile Acids

Gut bacteria influence the synthesis and metabolism of neuroactive lipids and bile acids that affect brain function through multiple mechanisms (see Figure 3).[61] Secondary bile acids produced by bacterial 7α-dehydroxylation cross the BBB and bind to nuclear receptors that regulate gene expression in neural tissues.[62,63] Specific bacterial strains capable of bile acid metabolism show associations with depression risk and treatment response.

Tryptophan Metabolite Effects

Microbial tryptophan metabolites, including indole-3-propionic acid and indole-3-aldehyde, influence synaptic function through aryl hydrocarbon receptor activation and anti-inflammatory effects.[55] These metabolites promote microglial anti-inflammatory phenotypes and support synaptic maintenance and plasticity (see Figure 3).

Neurotransmitter-Mediated Plasticity

Microbially-produced neurotransmitters influence synaptic plasticity through both direct and indirect mechanisms.

While these neurotransmitters may not directly cross the BBB, they influence vagal signaling and PNS function, indirectly modulating CNS plasticity.[64] Gut microbes function as a decentralized neurochemical factory, producing and metabolizing key neurotransmitters that shape mood, cognition, and behavior. Gut bacteria, spore-forming members of the *Clostridia* spices stimulate enterochromaffin cells to ramp up tryptophan hydroxylase-1 and boost serotonin synthesis,[65] while *Enterococcus, Streptococcus* and *Lactobacillus* species further support serotonin production by providing critical enzymes and substrate availability.[66] Given that roughly 90% of our serotonin originates in the gut, these microbial processes can meaningfully sway central serotonergic tone and thus impact mood regulation.

Parallel to serotonin, the GABAergic pathway is under microbial control. Genera such as *Lactobacillus, Bifidobacterium* and *Bacteroides* synthesize GABA, the brain's chief inhibitory neurotransmitter.[67] Clinical data show that supplementing GABA-producing probiotics lowers anxiety scores and moderates stress responses, highlighting a direct gut–brain route for calming hyperarousal and rebalancing HPA axis activity.[120] Certain *Bacillus* and *Serratia* species produce dopamine and its precursor L-DOPA, offer a microbial contribution to reward, motivation, and vulnerability to addiction.[14]

Together, these diverse microbial neurotransmitter pathways underscore the microbiome's central role in neuropsychiatric health and highlight targeted microbial therapies as promising adjuncts for mood, anxiety, and cognitive disorders.

NEUROPLASTICITY AND SYNAPTIC FUNCTION INFLUENCED BY GUT BACTERIA

As claimed by Agnihotri & Mohajeri,[68] the gut microbiome significantly influences the production and signaling of neurotrophic factors that regulate neurogenesis, dendritic morphology, neuroplasticity, neuronal survival, neuronal circuitry and synaptic function. Brain derived neurotrophic factor (BDNF), the most abundant neurotrophic factor in the brain, is modulated by multiple microbial metabolites and inflammatory mediators. *Lactobacillus helveticus* and *Bifidobacterium longum* have been shown in animal studies to enhance BDNF expression in the hippocampus and cortical regions, likely through their anti-inflammatory actions and their role in supporting gut barrier integrity. While SCFAs may contribute indirectly to these neuroprotective effects, the primary mechanisms appear to involve modulation of immune signaling and reduction of pro-inflammatory cytokines.

Glial Cell Modulation

According to Anbalagan,[69] the gut microbiota exerts a vital influence on glial cells (including microglia, astrocytes, and oligodendrocytes). These glial cells are essential for neuronal integrity, synaptic plasticity, and the maintenance of healthy neural circuits. Gut dysbiosis can impair these glial functions, leading to structural and functional neuronal abnormalities (see Figure 4). For example, altered microglial activity may result in excessive synaptic pruning, changes in dendritic spine architecture, and disrupted circuit formation. Dysbiosis also appears to affect oligodendrocyte-driven myelination, slowing neuronal signal transmission, and can compromise astrocyte regulation of BBB integrity, particularly under conditions of heightened inflammation. Gut-derived lipopolysaccharides further drives microglia toward pro-inflammatory states, enhancing cytokine production, reducing synaptic support, and accelerating synaptic elimination. This contributes to depressive behaviors, cognitive deficits, and diminished neuroplasticity through pathways involving reduced BDNF and heightened inflammatory signaling.

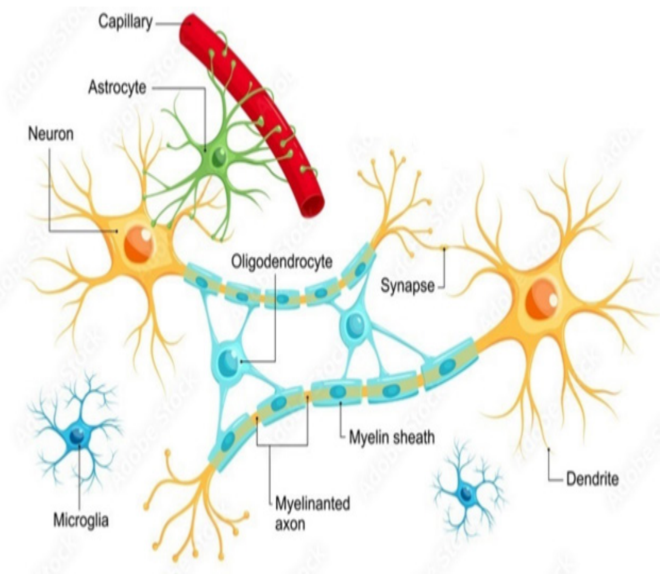

Figure 4. Glial cells and functions

In contrast, beneficial microbial metabolites such as SCFAs and tryptophan-derived compounds encourage microglia to adopt anti-inflammatory, neuroprotective states that help preserve synaptic plasticity and neuronal integrity.[70] These discoveries emphasize how the gut microbiome helps regulate the brain's immune environment, with significant consequences for mental health and resilience against neuropsychiatric disorders.

GUT MICROBIOME ALTERATIONS IN PSYCHIATRIC DISORDERS

Psychiatric disorders affect over 970 million people globally, with substantial personal, social, and economic costs that continue to rise despite advances in treatment.[71,72] In the study conducted by Mitrea and her team,[73] their findings show that MDD, anxiety disorders, SSD, BD, and ASD are all distinct from each other, yet their overlapping patterns of gut microbiome alterations contribute to their pathophysiology through the gut-brain axis. In MDD, studies consistently report reduced microbial diversity, lower levels of beneficial bacteria such as *Faecalibacterium*, *Coprococcus*, and *Dialister*, and an increase in pathogenic species like *Eggerthella*. These changes result in decreased production of SCFAs (e.g., butyrate), compromising BBB integrity and lowering BDNF levels.[74] The changes also result in an increase in lipopolysaccharide-producing bacteria fuel neuroinflammation and disrupt serotonin synthesis via activation of the kynurenine pathway. Anxiety disorders are linked to reductions in GABA-producing bacteria like

Lactobacillus and *Bifidobacterium*, alongside increases in pro-inflammatory species such as *Escherichia*. These imbalances contribute to heightened stress responses, altered neurotransmitter regulation and HPA axis dysregulation. Probiotic interventions targeting these microbial deficits have shown promise in reducing anxiety symptoms and enhancing stress resilience.[68]

In schizophrenia and psychotic disorders, patients typically exhibit reduced microbial diversity, disrupted tryptophan metabolism, and increased intestinal permeability. These gut changes contribute to dopaminergic dysfunction, immune activation, and metabolic disturbances that correlate with the severity of psychiatric symptoms. Antipsychotic medications further disrupt gut microbiota composition, sometimes exacerbating metabolic side effects such as weight gain.[73]

BD displays dynamic microbiome patterns that shift between manic and depressive states, with unique alterations in bacterial species involved in circadian rhythm regulation and inflammation.[74] Meanwhile, ASD is characterized by some of the most pronounced gut-brain axis disruptions, with marked reductions in beneficial bacteria, increased pathogenic species, and a high prevalence of gastrointestinal symptoms. Across these conditions, gut microbiome dysregulation emerges as a key factor in neuroinflammation, neurotransmitter imbalance, and metabolic dysfunction, pointing to the potential of microbiome-targeted therapies as promising adjunctive strategies.[75]

HPA Axis Dysregulation in Psychiatric Disorders

Chronic hyperactivation of the HPA axis, commonly seen in psychiatric disorders, leads to sustained cortisol elevation, hippocampal atrophy, reduced BDNF levels, and impaired stress adaptation.[76] Evidence suggests that inflammatory signals from gut dysbiosis, particularly elevated lipopolysaccharide and pro-inflammatory cytokines, are key contributors to this cascade, sustaining HPA dysfunction and neurodegeneration (see Figure 5).[77] When this microbial imbalance increases intestinal permeability ("leaky gut"), bacterial lipopolysaccharides can leak into the bloodstream, triggering a persistent inflammatory response. Pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are then able to cross the BBB, impairing neuroplasticity and neuronal health and thereby contributing to depressive symptoms.[78,79] They also disrupt neural networks involved in emotion regulation, memory, and cognition. For instance, elevated peripheral cytokines in depression and stress-related disorders have been linked to dysfunction in corticolimbic circuits, including the prefrontal cortex and hippocampus, leading to emotional and cognitive deficits.

Anxiety disorders similarly show excessive HPA activity, where microbiome-induced inflammation and loss of beneficial bacteria amplify stress responses and cortisol secretion.[80] In MDD, SSD, and BD, leaky gut facilitates microbial translocation, resulting in systemic inflammation that further perpetuates HPA-axis hyperactivity and heightens vulnerability to stress and symptom severity. In ASD, early-life HPA hyperreactivity is frequently seen, with gut-derived inflammatory triggers contributing to heightened stress sensitivity and poor glucocorticoid feedback control. In all these conditions, gut dysbiosis amplifies HPA dysfunction through immune activation, loss of SCFA-mediated regulation, and disrupted neuroendocrine feedback loops.[81]

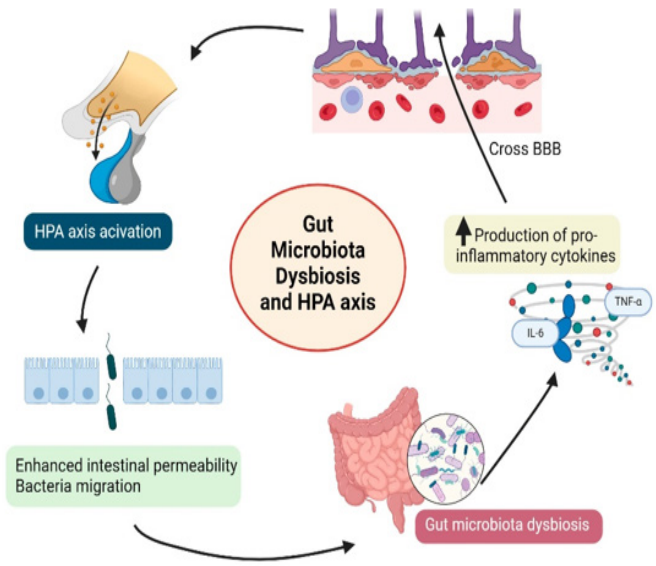

Figure 5. HPA dysregulation and gut dysbiosis
HPA: Hypothalamic pituitary adrenal

By integrating these insights, we gain a more comprehensive understanding of MDD's underlying biology and open the door to multifaceted treatment strategies. Techniques to recalibrate HPA axis function such as stress-management practices and cognitive behavioral therapy (CBT), promises a more holistic approach to both preventing and managing depression.[82] Ultimately, a collaborative, body-mind treatment paradigm may offer the greatest promise for alleviating this challenging condition.

Circadian Rhythm Disruption Association with Gut Microbiome in Psychiatric Disorders

Circadian rhythm (see Figure 6)[83] disruption and misalignment manifests as disturbed sleep-wake cycles, altered melatonin production, and flattened cortisol rhythms across MDD, BD, SSD and anxiety disorder, is a pervasive feature deeply intertwined with mood, cognition, and behavior. Insomnia is a common and clinically important feature across several psychiatric disorders, often both a symptom and a contributing factor to illness severity.[84] Circadian disruption decouples the synchronized daily rhythms of the gut microbiome, promoting dysbiosis and barrier dysfunction. These changes trigger inflammation and metabolic imbalance and potentially worsen neuropsychiatric symptoms. Dysbiotic gut microbiota, which normally show diurnal oscillations and influence peripheral clock gene expression, lose this synchrony in these conditions, further desynchronizing the central and peripheral clocks.[85]

Substance Addiction in Psychiatric Disorders

The co-occurrence of psychiatric disorders and substance use disorders (SUDs) remains a major challenge in mental health care, with around half of individuals diagnosed with one also experiencing the other. This overlap is especially pronounced in serious mental illnesses such as SSD, BD, ADHD and MDD.[86] Individuals may turn to substances to alleviate symptoms of a psychiatric disorder, while substance use can

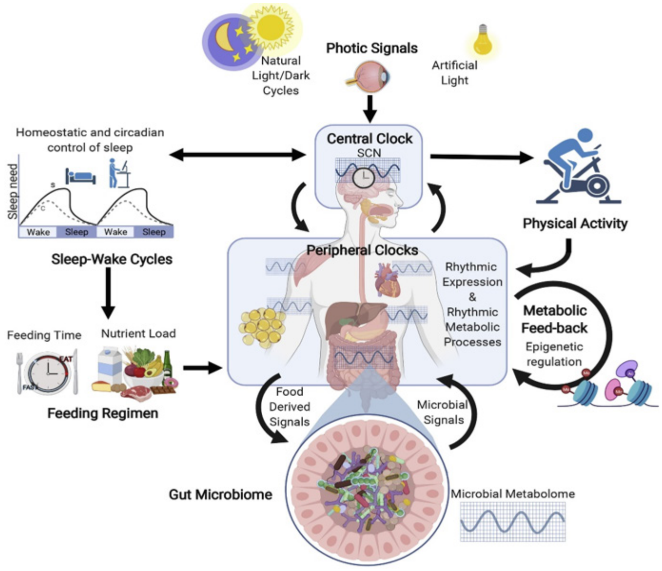

Figure 6. Circadian rhythm and gut microbiome synchrony

itself trigger or exacerbate mental health conditions. These combined comorbid conditions lead to more complicated diagnoses, lower rates of recovery, higher relapse risk, and greater strain on treatment systems.[87]

According to Martinez and his team,[88] smoking, heavy alcohol use, and other substance abuse frequently induce gut dysbiosis through direct chemical effects on microbiota, epithelial damage, and immune activation. These changes can be persistent, although lifestyle modifications like smoking cessation or non-pharmacological therapies (e.g., behavioural therapy and probiotics) have shown promise in partially reversing dysbiosis and related health impacts.

NON-PHARMACOLOGICAL THERAPEUTIC INTERVENTIONS

Psychiatric medications (or pharmacotherapy), while essential in many treatment plans, can inadvertently disrupt gut health. For instance, second-generation antipsychotics (SGAs; e.g., risperidone and aripiprazole) are associated with reduced microbial diversity and shifts in key bacterial phyla, typically decreasing *Firmicutes* and *Actinobacteria*, while increasing Proteobacteria.[89,90] These microbial changes lead to diminished short-chain fatty acid (SCFA) production, compromising gut barrier function and contributing to metabolic side effects like weight gain, hyperlipidemia, and insulin resistance. Similarly, SSRIs like fluoxetine and citalopram have been shown to deplete beneficial genera such as *Lactobacillus*, *Bifidobacterium*, and *Ruminococcus*, while promoting proliferation of *Enterobacteriaceae*.[91] Given these challenges, non-pharmacological interventions targeting gut–brain mechanisms have gained prominence.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) involves the transfer of fecal material from a screened healthy donor to a recipient with dysbiosis. The transfer can be accomplished through several routes, including colonoscopy (allowing direct delivery to the colon), upper gastrointestinal endoscopy (delivering to the duodenum or jejunum), nasogastric or nasoduodenal tubes, oral capsules containing lyophilized or frozen fecal material, or enema administration. Recent advances have made oral encapsulated FMT increasingly popular due to its non-invasive nature and comparable efficacy to colonoscopic delivery for certain indications, with frozen or freeze-dried preparations showing similar success rates. The choice of delivery method depends on factors including the target intestinal location, patient tolerance, clinical indication, and institutional protocols, with upper GI delivery potentially offering advantages for small intestinal colonization while lower GI routes may better establish colonic microbiota.

Originally developed for refractory *Clostridioides difficile* infections, FMT is now being explored for its neuropsychiatric implications, especially in disorders involving gut-brain axis disruptions.[92] Preliminary evidence suggests FMT may improve gastrointestinal and behavioral symptoms, although the precise microbial profiles required for optimal psychiatric benefit remain unclear. Longitudinal, placebo-controlled trials are needed to refine donor selection criteria, administration protocols, and define target microbiome signatures linked to mental health outcomes.[52]

Dietary and Psychobiotic Interventions

Dietary modification is one of the most accessible and modifiable interventions for gut-brain health. High-fibre diets help to enhance SCFA production, strengthen gut barrier integrity, and reduce systemic inflammation.[93,94] The Mediterranean diet, which is rich in vegetables, whole grains, polyphenols, and omega-3 fatty acids, has demonstrated efficacy in reducing depressive and anxiety symptoms.[95] For individuals with gastrointestinal sensitivities, elimination diets or low-FODMAP protocols can help identify triggers that exacerbate both GI and psychiatric symptoms.

The emerging field of psychobiotics focuses on specific probiotic strains with mental health benefits. For example, *Lactobacillus helveticus* and *Bifidobacterium longum* have shown anxiolytic and antidepressant effects in clinical studies.[68] Personalized psychobiotic therapy, guided by microbiome profiles and host genetic markers, provides a promising future intervention approach.[96]

Prebiotics (e.g., inulin or galacto-oligosaccharides) nourish beneficial bacteria and suppress pathogenic strains. Supplementation with prebiotics has shown particular benefit in stress-related disorders and mild-to-moderate anxiety.[97] Synbiotic interventions, which combine probiotics and prebiotics, provide a dual mechanism, delivering beneficial microbes while enhancing their survival and colonization. Together, these microbiome-targeted strategies may offer additive or synergistic benefits in complex psychiatric presentations.[98,99]

Educational Therapy (EdTx)

EdTx, long endorsed by the WHO,[100] plays a foundational role in empowering patients to understand the biological and lifestyle factors influencing their mental health. In this context, EdTx includes structured psychoeducation around the gut–brain axis, helping individuals comprehend how dietary choices, stress, inflammation, and microbial balance interact to influence mood, cognition, and systemic health.[101]

Core components of EdTx also address chronobiology and stress physiology. Techniques such as mindfulness-based stress reduction (MBSR), which incorporates breathwork, body scanning, and mindful movement, have been shown to reduce salivary cortisol levels and improve emotional regulation.[102] Similarly, cognitive appraisal training helps individuals reframe maladaptive stress responses, lowering cortisol reactivity during acute stress exposures.[103]

Chrono-education, another pillar of EdTx, teaches patients about the biological importance of maintaining regular sleep–wake cycles, consistent meal timing, and exposure to natural light.[104] These strategies promote dim-light melatonin onset, stabilize hormonal rhythms, and support sleep hygiene.[105] When paired with diet literacy, such as understanding the benefits of high-fibre and fermented foods, EdTx equips patients with the tools to make informed, sustainable changes.

Mental Wellness & Behavior Therapy (MWBT)

Behavioral therapy (BeTx) and mental wellness techniques (MWTech) complement EdTx by translating knowledge into action. Interventions, e.g., CBT,[106] behavioral activation (a form of short-term out-patient therapy),[107] and acceptance and commitment therapy (ACT),[108] target maladaptive behaviors like emotional eating, irregular meal patterns, and sleep dysregulation. Notably, a study in patients with irritable bowel syndrome (IBS) showed that CBT not only improved GI and mood symptoms but also led to shifts in gut microbiota and brain connectivity, highlighting the bi-directional influence of psychological therapy on gut–brain physiology.[82]

Further, mindfulness-based techniques, yoga, and group-based interventions foster vagal tone and reduce stress-induced microbial disruptions.[109,110] For example, CBT for insomnia (CBT-I) has been shown in meta-analyses to improve sleep latency and efficiency, while normalizing nocturnal cortisol rhythms.[111] MBSR protocols have also demonstrated reductions in inflammatory markers such as IL-6 in both clinical and non-clinical populations.

Lifestyle Coaching and Circadian Health

Lifestyle coaching supports the sustained adoption of behavior changes by integrating personalized strategies that align with circadian and microbiome rhythms. Time-restricted feeding (limiting daily food intake to an 8-10 hour window) can restore microbial diurnal oscillations, enhance metabolic health, and regulate clock gene expression.[112] Similarly, morning bright-light therapy helps entrain circadian rhythms by activating the suprachiasmatic nucleus, improving sleep–wake cycles, and reducing depressive symptoms.[113]

Physical activity, especially in the morning, not only promotes sleep consolidation but also enhances microbiome diversity and circadian stability. Coaching patients on practical steps such as fixed bedtimes, reducing caffeine/alcohol intake before sleep, limiting daytime naps, and optimizing sleep environments (cool, dark, and quiet) can support long-term autonomic balance and gut–brain harmony.

Integrative Framework and Outcomes

Taken together, these non-pharmacological interventions form a robust, integrative model comprising four interdependent domains: (i) EdTx, which builds the foundational understanding and motivation around gut-brain health; (ii) behavior therapy (BeTx), which installs actionable, sustainable lifestyle changes; iii) mental Wellness techniques (MWTech), which supports emotional regulation, stress resilience, and autonomic balance; and (iv) microbiome science (MbSc), which anchors all interventions in evidence-based biological mechanisms. The authors of this paper have termed it biopsychosocial-educational (BPSE) model (see Figure 7).

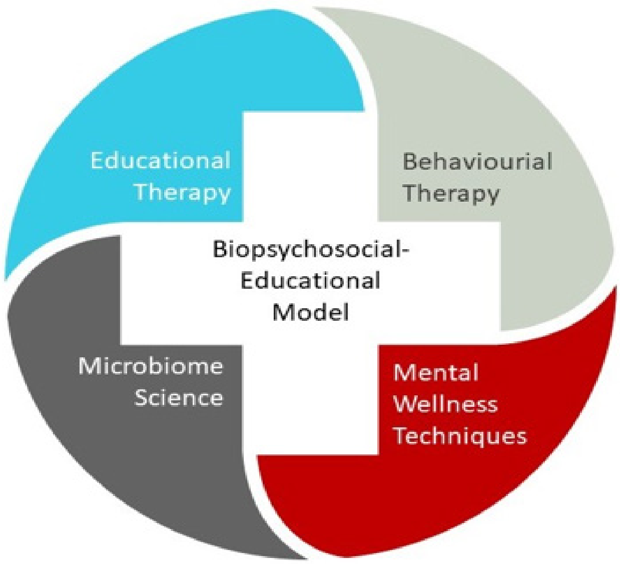

Figure 7. The biopsychosocial-educational (BPSE) model

This BPSE framework is particularly suited for populations with IBS and anxiety, mood disorders with metabolic features, or neurodevelopmental conditions, e.g., in the context of ASD, where the gut-brain axis plays a pronounced role.[114] The outcomes from such integrated care models can be measured across multiple domains, e.g., (i) psychiatric symptoms: can improve scores on PHQ-9[115] and/or GAD-7,[116] for example; (ii) GI symptoms: can be tracked via IBS-SSS and stool form scales;[117] (iii) Behavioral and cognitive functioning: can enhance executive function and consistency in self-care;[118] and (iv) microbiome health: can increase in beneficial taxa (e.g., *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium prausnitzii*), and corresponding reductions in inflammation. By bridging cognitive, emotional, behavioral, and biological domains, this BPSE model empowers patients to actively participate in their own healing process and fosters sustainable, whole-person wellness.[119]

CONCLUSION

The gut microbiome represents a paradigm shift in understanding psychiatric disorders, revealing complex bidirectional relationships between microbial communities and brain functions. The evidence consistently demonstrates that gut dysbiosis is associated with various mental health conditions, with mechanistic pathways involving neural signalling, metabolite production, immune modulation associated with stress response system, circadian rhythm, nutritional options, lifestyle habits and substance addiction.

The association between intestinal bacterial diversity and psychiatric or neurological diseases represents a complex bidirectional relationship rather than a unidirectional causal pathway. Emerging evidence demonstrates that gut dysbiosis may function as a contributory etiological factor through several mechanisms: microbial synthesis of neurotransmitters and neuroactive metabolites that modulate CNS function, bacterial metabolite-mediated regulation of systemic inflammation and BBB integrity, and vagal nerve transmission of gut-derived signals that influence mood, cognition, and behavior.

Conversely, psychiatric and neurological conditions reciprocally alter gut microbiome composition through multiple pathways. Chronic psychological stress induces HPA axis hyperactivation and sustained cortisol elevation, directly disrupting microbial ecosystems. Mental illness-associated behavioral changes, including altered dietary patterns, reduced physical activity, and sleep disruption that substantially reshape the microbiome. Additionally, psychotropic medications exert antimicrobial effects that modify bacterial communities, while autonomic dysfunction in neurological disorders affects gastrointestinal motility and secretion, creating selective pressures on microbial populations. This creates a self-reinforcing cycle wherein initial dysbiosis increases neuropsychiatric vulnerability, while the disease state subsequently exacerbates microbial imbalance through behavioral, neuroendocrine, and pharmacological mechanisms.

The therapeutic implications of gut-brain axis research extend far beyond traditional pharmacological approaches to include personalized interventions targeting microbiome optimization. The integration of microbiome science with non-pharmacological intervention such as EdTx, CBT, MBSR, FMT, dietary options and psychobiotic intervention may offers unprecedented new opportunities for precision medicine approaches that consider individual biological profiles when selecting treatments.

These clinical implementations must also address regulatory considerations, healthcare provider education, and economic factors that will influence widespread adoption of microbiome-based therapeutics. This implementation will likely include routine assessment of gut microbiome status alongside traditional clinical evaluations, with treatment plans incorporating both conventional therapies and microbiome-targeted interventions. This integrated approach holds promise for improving treatment outcomes while reducing side effects and healthcare costs. The gut-brain axis represents one of the most exciting frontiers in mental health research, offering hope for more effective, personalized treatments that address the underlying biological mechanisms of psychiatric disorders and addiction. Continued investment in this research area will be essential for translating scientific discoveries into clinical benefits for patients worldwide.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

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REFERENCES

1. Salvadori M, Rosso G. Update on the gut microbiome in health and diseases. *World J Methodol.* 2024;14(1):89196. doi:10.5662/wjm.v14.i1.89196
2. Sharma B, Kumar A, Sharma U, Pal D, Prashar S. The potential role of gut microbiota in the pathogenesis of type 2 diabetes mellitus via epigenetics and inflammasome. *Endocr Metab Immune Disord Drug Targets.* 2022;22(14):1331-1343. doi:10.2174/1871530322666220331152809
3. Glinert A, Turjeman S, Elliott E, Koren O. Microbes, metabolites and (synaptic) malleability, oh my! The effect of the microbiome on synaptic plasticity. *Biol Rev Camb Philos Soc.* 2022;97(2):582-599. doi:10.1111/brv.12812
4. Dash S, Syed YA, Khan MR. Understanding the role of the gut microbiome in brain development and its association with neurodevelopmental psychiatric disorders. *Front Cell Dev Biol.* 2022;10:880544. doi:10.3389/fcell.2022.880544
5. Fock E, Parnova R. Mechanisms of blood-brain barrier protection by microbiota-derived short-chain fatty acids. *Cells.* 2023;12(4):657. doi:10.3390/cells12040657
6. Sarkar A, Harty S, Johnson KV, et al. The role of the microbiome in the neurobiology of social behaviour. *Biol Rev Camb Philos Soc.* 2020;95(5):1131-1166. doi:10.1111/brv.12603
7. Singh H, Chopra C, Singh H, et al. Gut-brain axis and Alzheimer's disease: Therapeutic interventions and strategies. *J Functional Foods.* 2024;112:105915. doi:10.1016/j.jff.2023.105915
8. Ma L, Wang HB, Hashimoto K. The vagus nerve: an old but new player in brain-body communication. *Brain Behav Immun.* 2025;124:28-39. doi:10.1016/j.bbi.2024.11.023
9. Magalhães HIR, Castelucci P. Enteric nervous system and inflammatory bowel diseases: correlated impacts and therapeutic approaches through the P2X7 receptor. *World J Gastroenterol.* 2021;27(46):7909-7924. doi:10.3748/wjg.v27.i46.7909
10. Sharkey KA, Mawe GM. The enteric nervous system. *Physiol Rev.* 2023;103(2):1487-1564. doi:10.1152/physrev.00018.2022
11. Mayer EA, Nance K, Chen S. The gut-brain axis. *Annu Rev Med.* 2022;73:439-453. doi:10.1146/annurev-med-042320-014032
12. Yassin LK, Nakhal MM, Alderei A, et al. Exploring the microbiota-gut-brain axis: impact on brain structure and function. *Front Neuroanat.* 2025;19:1504065. doi:10.3389/fnana.2025.1504065
13. Zang Y, Lai X, Li C, Ding D, Wang Y, Zhu Y. The role of gut microbiota in various neurological and psychiatric disorders-an evidence mapping based on quantified evidence. *Mediators Inflamm.* 2023;2023:5127157. doi:10.1155/2023/5127157
14. Dicks LMT. Gut bacteria and neurotransmitters. *Microorganisms.* 2022;10(9):1838. doi:10.3390/microorganisms10091838
15. De Sales-Millán A, Aguirre-Garrido JF, González-Cervantes RM, Velázquez-Aragón JA. Microbiome-gut-mucosal-immune-brain axis and autism spectrum disorder (ASD): a novel proposal of the role of the gut microbiome in ASD aetiology. *Behav Sci (Basel).* 2023;13(7):548. doi:10.3390/bs13070548

16. Wong GC, Montgomery JM, Taylor MW. The gut-microbiota-brain axis in autism spectrum disorder. In: Grabrucker AM, editor. Autism Spectrum Disorders [Internet]. Brisbane (AU): Exon Publications; 2021. doi:10.36255/exonpublications.autismspectrumdisorders.2021.gutmicrobiota
17. Boehme M, Rémond-Derbez N, Lerond C, et al. Bifidobacterium longum subsp. longum reduces perceived psychological stress in healthy adults: an exploratory clinical trial. *Nutrients*. 2023;15(14):3122. doi:10.3390/nu15143122
18. Alatan H, Liang S, Shimodaira Y, et al. Supplementation with *Lactobacillus helveticus* NS8 alleviated behavioral, neural, endocrine, and microbiota abnormalities in an endogenous rat model of depression. *Front Immunol*. 2024;15:1407620. doi:10.3389/fimmu.2024.1407620
19. Boustany A, Feuerstadt P, Tillotson G. The 3 Ds: depression, dysbiosis, and*Clostridiodes* difficile. *Adv Ther*. 2024;41:3982-3995 doi:10.1007/s12325-024-02972-0
20. Dunlop BW, Cha J, Mayberg HS, et al. Association of bile acids with connectivity of executive control and default mode networks in patients with major depression. *bioRxiv [Preprint]*. 2024:2024.12.20.629637. doi:10.1101/2024.12.20.629637
21. Dziedzic A, Maciak K, Bliźniewska-Kowalska K, Gałecka M, Kobierecka W, Saluk J. The power of psychobiotics in depression: a modern approach through the microbiota-gut-brain axis: a literature review. *Nutrients*. 2024;16(7):1054. doi:10.3390/nu16071054
22. Giuliano G, Benedetti S, Sambo M, Pierguidi F, Tumbarello M. Successful treatment of complicated infective endocarditis due to *Enterococcus faecium* in a patient with substance use disorder using oritavancin as sequential maintenance therapy. *Clin Microbiol Infect*. 2024;30(4):556-557. doi:10.1016/j.cmi.2024.01.008
23. Ioannou M, Borkent J, Andreu-Sánchez S, et al. Reproducible gut microbial signatures in bipolar and schizophrenia spectrum disorders: a metagenome-wide study. *Brain Behav Immun*. 2024;121:165-175. doi:10.1016/j.bbi.2024.07.009
24. Khaledi M, Sameni F, Gholipour A, et al. Potential role of gut microbiota in major depressive disorder: a review. *Heliyon*. 2024;10(12):e33157. doi:10.1016/j.heliyon.2024.e33157
25. Nirmalkar K, Patel J, Kang DW, et al. (2024). Bimodal distribution of intestinal *Candida* in children with autism and its potential link with worse ASD symptoms. *Gut Microbes Reports*. 2024;1(1):2358324. doi:10.1080/29933935.2024.2358324
26. Rishi P, Kaur A, Kaur H. COVID-19 Pandemic and Mental Illness: Impact of Gut Microbiota. In: Sobti, R.C., Dhalla, N.S., Watanabe, M., Sobti, A. (eds) Delineating health and health system: mechanistic insights into COVID 19 complications. Springer, Singapore. 2021. doi:10.1007/978-981-16-5105-2_20
27. Xu J, Zhou L, Chen Z, et al. *Bacillus coagulans* and *Clostridium butyricum* synergistically alleviate depression in a chronic unpredictable mild stress mouse model through altering gut microbiota and prefrontal cortex gene expression. *Front Pharmacol*. 2024;15:1393874. doi:10.3389/fphar.2024.1393874
28. Zhang L, Shao Y, Li Y, et al. Epidemiological and molecular investigations of sequential outbreaks of *Campylobacter jejuni* infecting adults and schoolchildren in Southeastern China, 2021-2022. *Int J Infect Dis*. 2024;144:107055. doi:10.1016/j.ijid.2024.107055
29. Zhao J, Liu J, Feng J, Liu X, Hu Q. The gut microbiota-brain connection: insights into major depressive disorder and bipolar disorder. *Front Psychiatry*. 2024;15:1421490. doi:10.3389/fpsyt.2024.1421490
30. Levine BH, Hoffman JM. Gut microbiome transplants and their health impacts across species. *Microorganisms*. 2023;11(6):1488. doi:10.3390/microorganisms11061488
31. Levkova M, Chervenkov T, Pancheva R. Genus-level analysis of gut microbiota in children with autism spectrum disorder: a mini review. *Children (Basel)*. 2023;10(7):1103. doi:10.3390/children10071103
32. Lewandowska-Pietruszka Z, Figlerowicz M, Mazur-Melewska K. Microbiota in autism spectrum disorder: a systematic review. *Int J Mol Sci*. 2023;24(23):16660. doi:10.3390/ijms242316660
33. Li H, Liu C, Huang S, et al. Multi-omics analyses demonstrate the modulating role of gut microbiota on the associations of unbalanced dietary intake with gastrointestinal symptoms in children with autism spectrum disorder. *Gut Microbes*. 2023;15(2):2281350. doi:10.1080/19490976.2023.2281350
34. Ramirez Garcia A, Greppi A, Constancias F, et al. *Anaerobutyricum hallii* promotes the functional depletion of a food carcinogen in diverse healthy fecal microbiota. *Frontiers in Microbiomes*. 2023;2:1194516. doi:10.3389/frmbi.2023.1194516
35. Rashnaei N, Akhavan Sepahi A, Siadat SD, Shahsavand-Ananloo E, Bahramali G. Characterization of gut microbiota profile in Iranian patients with bipolar disorder compared to healthy controls. *Front Cell Infect Microbiol*. 2023;13:1233687. doi:10.3389/fcimb.2023.1233687
36. Tamés H, Sabater C, Margolles A, Ruiz L, Ruas-Madiedo P. Production of GABA in milk fermented by *Bifidobacterium adolescentis* strains selected on the bases of their technological and gastrointestinal performance. *Food Res Int*. 2023;171:113009. doi:10.1016/j.foodres.2023.113009
37. Daneberga Z, Nakazawa-Miklasevica M, Berga-Svitina E, et al. Urinary organic acids spectra in children with altered gut microbiota composition and autistic spectrum disorder. *Nord J Psychiatry*. 2022;76(7):523-529. doi:10.1080/08039488.2021.2014954
38. Elwakil BH, Bakr BA, Aljeldah MM, et al. Memory impairment, pro-inflammatory host response and brain histopathologic severity in rats infected with *K. pneumoniae* or *P. aeruginosa* meningitis. *Pathogens*. 2022;11(8):933. doi:10.3390/pathogens11080933.
39. Gkougka D, Mitropoulos K, Tzanakaki G, et al. Gut microbiome and attention deficit/hyperactivity disorder: a systematic review. *Pediatr Res*. 2022;92(6):1507-1519. doi:10.1038/s41390-022-02027-6
40. Glover JS, Browning BD, Ticer TD, Engevik AC, Engevik MA. *Acinetobacter calcoaceticus is* well adapted to withstand intestinal stressors and modulate the gut epithelium. *Front Physiol*. 2022;13:880024. doi:10.3389/fphys.2022.880024
41. Kakabadze E, Makalatia K, Bakuradze N, et al. (2022). Gut health of children with autism spectrum disorder. *World Academy Sci J*. 2022;4:29. doi:10.3892/wasj.2022.164
42. Liu Q, Mak JWY, Su Q, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut*. 2022;71(3):544-552. doi:10.1136/gutjnl-2021-325989.
43. Raghavan K, Dedeepiya VD, Yamamoto N, et al. Benefits of gut microbiota reconstitution by beta 1,3–1,6 glucans in subjects with autism spectrum disorder and other neurodegenerative diseases. *J Alzheimer's Disease*. 2022;94(s1):S241-S252. doi:10.3233/JAD-220388
44. Son J, Baritugo KA, Sohn YJ, et al. Production of γ-aminobutyrate (GABA) in recombinant corynebacterium glutamicum by expression of glutamate decarboxylase active at neutral pH. *ACS Omega*. 2022;7(33):29106-29115. doi:10.1021/acsomega.2c02971
45. Zhang F, Zhou Y, Chen H, et al. Curcumin alleviates DSS-induced anxiety-like behaviors via the microbial-brain-gut axis. *Oxid Med Cell Longev*. 2022;2022:6244757. doi:10.1155/2022/6244757
46. Agarwala S, Naik B, Ramachandra NB. Mucosa-associated specific bacterial species disrupt the intestinal epithelial barrier in the autism phenome. *Brain Behav Immun Health*. 2021;15:100269. doi:10.1016/j.bbih.2021.100269
47. Elwishahy A, Antia K, Bhusari S, Ilechukwu NC, Horstick O, Winkler V. Porphyromonas gingivalis as a risk factor to Alzheimer's disease: a systematic review. *J Alzheimers Dis Rep*. 2021;5(1):721-732. doi:10.3233/ADR-200237
48. Ezeji JC, Sarikonda DK, Hopperton A, et al. *Parabacteroides distasonis:* intriguing aerotolerant gut anaerobe with emerging antimicrobial resistance and pathogenic and probiotic roles in human health. *Gut Microbes*. 2021;13(1):1922241. doi:10.1080/19490976.2021.1922241
49. Jeong J, Lee Y, Yoon S, Kim JH, Kim W. *Lactiplantibacillus plantarum* LRCC5314 includes a gene for serotonin biosynthesis via the tryptophan metabolic pathway. *J Microbiol*. 2021;59(12):1092-1103. doi:10.1007/s12275-021-1472-2
50. Knuesel T, Mohajeri MH. The role of the gut microbiota in the development and progression of major depressive and bipolar disorder. *Nutrients*. 2021;14(1):37. doi:10.3390/nu14010037
51. Szopinska-Tokov J, Dam S, Naaijen J, et al. Investigating the gut microbiota composition of individuals with attention-deficit/hyperactivity disorder and association with symptoms. *Microorganisms*. 2020;8(3):406. doi:10.3390/microorganisms8030406
52. Zuffa S, Schimmel P, Gonzalez-Santana A, et al. Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder. *Transl Psychiatry*. 2023;13(1):257. doi:10.1038/s41398-023-02556-6
53. Jayapala HPS, Lim SY. N-3 polyunsaturated fatty acids and gut microbiota. *Comb Chem High Throughput Screen*. 2023;26(5):892-905. doi:10.2174/1386207325666220701121025
54. Matsumura Y, Kitabatake M, Kayano SI, Ito T. Dietary phenolic compounds: their health benefits and association with the gut microbiota. *Antioxidants (Basel)*. 2023;12(4):880. doi:10.3390/antiox12040880
55. Salminen A. Activation of aryl hydrocarbon receptor (AhR) in Alzheimer's disease: role of tryptophan metabolites generated by gut host-microbiota. *J Mol Med (Berl)*. 2023;101(3):201-222. doi:10.1007/s00109-023-02289-5
56. Zhao X, Kong M, Wang Y, et al. *Nicotinamide mononucleotide* improves the Alzheimer's disease by regulating intestinal microbiota. *Biochem Biophys Res Commun*. 2023;670:27-35. doi:10.1016/j.bbrc.2023.05.075

57. O'Riordan KJ, Collins MK, Moloney GM, et al. Short chain fatty acids: microbial metabolites for gut-brain axis signalling. *Mol Cell Endocrinol.* 2022;546:111572. doi:10.1016/j.mce.2022.111572
58. Yan Z, Yang F, Sun L, et al. Role of gut microbiota-derived branched-chain amino acids in the pathogenesis of Parkinson's disease: an animal study. *Brain Behav Immun.* 2022;106:307-321. doi:10.1016/j.bbi.2022.09.009
59. Gatarek P, Kaluzna-Czaplinska J. Trimethylamine N-oxide (TMAO) in human health. *EXCLI J.* 2021;20:301-319. doi:10.17179/excli2020-3239
60. Sokolovskaya OM, Shelton AN, Taga ME. Sharing vitamins: *Cobamides unveil* microbial interactions. *Science.* 2020;369(6499):eaba0165. doi:10.1126/science.aba0165
61. Recharla N, Geesala R, Shi XZ. Gut microbial metabolite butyrate and its therapeutic role in inflammatory bowel disease: a literature review. *Nutrients.* 2023;15(10):2275. doi:10.3390/nu15102275
62. Wise JL, Cummings BP. The 7-α-dehydroxylation pathway: an integral component of gut bacterial bile acid metabolism and potential therapeutic target. *Front Microbiol.* 2023;13:1093420. doi:10.3389/fmicb.2022.1093420
63. Kiriyama Y, Nochi H. Role of microbiota-modified bile acids in the regulation of intracellular organelles and neurodegenerative diseases. *Genes (Basel).* 2023;14(4):825. doi:10.3390/genes14040825
64. Aljeradat B, Kumar D, Abdulmuizz S, et al. Neuromodulation and the gut-brain axis: therapeutic mechanisms and implications for gastrointestinal and neurological disorders. *Pathophysiology.* 2024;31(2):244-268. doi:10.3390/pathophysiology31020019
65. Aizawa S, Uebanso T, Shimohata T, Mawatari K, Takahashi A. Effects of the loss of maternal gut microbiota before pregnancy on gut microbiota, food allergy susceptibility, and epigenetic modification on subsequent generations. *Biosci Microbiota Food Health.* 2023;42(3):203-212. doi:10.12938/bmfh.2022-093
66. Scardaci R, Manfredi M, Barberis E, Scutera S, Marengo E, Pessione E. Serotonin exposure improves stress resistance, aggregation, and biofilm formation in the probiotic *Enterococcus faecium* NCIMB10415. *Microbiology Research.* 2021;12(3):606-625. doi:10.3390/microbiolres12030043
67. Iorizzo M, Paventi G, Di Martino C. Biosynthesis of gamma-aminobutyric acid (GABA) by *Lactiplantibacillus plantarum* in fermented food production. *Curr Issues Mol Biol.* 2023;46(1):200-220. doi:10.3390/cimb46010015
68. Agnihotri N, Mohajeri MH. Involvement of intestinal microbiota in adult neurogenesis and the expression of brain-derived neurotrophic factor. *Int J Mol Sci.* 2022;23(24):15934. doi:10.3390/ijms232415934
69. Anbalagan S. Endocrine cross-talk between the gut microbiome and glial cells in development and disease. *J Neuroendocrinol.* 2021;33(5):e12924. doi:10.1111/jne.12924
70. Missiego-Beltrán J, Beltrán-Velasco AI. The role of microbial metabolites in the progression of neurodegenerative diseases-therapeutic approaches: a comprehensive review. *Int J Mol Sci.* 2024;25(18):10041. doi:10.3390/ijms251810041
71. Martinelli, A. Sustainable promotion of mental health and prevention of mental health disorders across the world. In: Rezaei, N. (eds) Integrated Science for Sustainable Development Goal 3. Integrated Science, vol 25. Springer, Cham. 2024. doi:10.1007/978-3-031-64288-3_1
72. GDB (Global Burden of Disease) Study: Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry.* 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3
73. Mitrea L, Nemeş SA, Szabo K, Teleky BE, Vodnar DC. Guts imbalance imbalances the brain: a review of gut microbiota association with neurological and psychiatric disorders. *Front Med (Lausanne).* 2022;9:813204. doi:10.3389/fmed.2022.813204
74. McGuinness AJ, Davis JA, Dawson SL, et al. A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia. *Mol Psychiatry.* 2022;27(4):1920-1935. doi:10.1038/s41380-022-01456-3
75. Puricelli C, Rolla R, Gigliotti L, et al. The gut-brain-immune axis in autism spectrum disorders: a state-of-art report. *Front Psychiatry.* 2022;12:755171. doi:10.3389/fpsyt.2021.755171
76. Numakawa T, Kajihara R. An interaction between brain-derived neurotrophic factor and stress-related glucocorticoids in the pathophysiology of Alzheimer's disease. *Int J Mol Sci.* 2024;25(3):1596. doi:10.3390/ijms25031596
77. Kiełbik P, Witkowska-Piłaszewicz O. The relationship between canine behavioral disorders and gut microbiome and future therapeutic perspectives. *Animals (Basel).* 2024;14(14):2048. doi:10.3390/ani14142048
78. Versele R, Sevin E, Gosselet F, Fenart L, Candela P. TNF-α and IL-1β modulate blood-brain barrier permeability and decrease amyloid-β peptide efflux in a human blood-brain barrier model. *Int J Mol Sci.* 2022;23(18):10235. doi:10.3390/ijms231810235
79. Grebenciucova E, VanHaerents S. Interleukin 6: at the interface of human health and disease. *Front Immunol.* 2023;14:1255533. doi:10.3389/fimmu.2023.1255533
80. Rusch JA, Layden BT, Dugas LR. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. *Front Endocrinol (Lausanne).* 2023;14:1130689. doi:10.3389/fendo.2023.1130689
81. Hoffman KW, Lee JJ, Corcoran CM, Kimhy D, Kranz TM, Malaspina D. Considering the microbiome in stress-related and neurodevelopmental trajectories to schizophrenia. *Front Psychiatry.* 2020;11:629. doi:10.3389/fpsyt.2020.00629
82. Jacobs JP, Gupta A, Bhatt RR, et al. Cognitive behavioral therapy for irritable bowel syndrome induces bidirectional alterations in the brain-gut-microbiome axis associated with gastrointestinal symptom improvement. *Microbiome.* 2021;9(1):236. doi:10.1186/s40168-021-01188-6
83. Gutierrez DE, Lashinger LM, Weinstock GM, Bray MS. Circadian rhythms and the gut microbiome synchronize the host's metabolic response to diet. *Cell Metab.* 2021;33(5):873-887. doi:10.1016/j.cmet.2021.03.015
84. Samanta S, Bagchi D. An intricate relationship between circadian rhythm dysfunction and psychiatric diseases. *Explor Neurosci.* 2024;3:321-351. doi:10.37349/en.2024.00053
85. Tran L, Shaikh M, Engen PA, et al. Impact of peripheral circadian misalignment and alcohol on the resiliency of intestinal barrier and microbiota. *Gut Microbes.* 2025;17(1):2509281. doi:10.1080/19490976.2025.2509281
86. Common Comorbidities with Substance Use Disorders Research Report. Bethesda (MD): National Institutes on Drug Abuse (US); April 2020.
87. Campêlo SR, Barbosa MA, Porto CC, Dias DR. Prevalence of comorbid substance use disorders with anxiety disorders or post-traumatic stress disorder in people seeking treatment for substance abuse: a systematic review protocol. *JBI Evid Synth.* 2021;19(8):1924-1933. doi:10.11124/JBIES-20-00267
88. Martinez JE, Kahana DD, Ghuman S, et al. Unhealthy lifestyle and gut dysbiosis: a better understanding of the effects of poor diet and nicotine on the intestinal microbiome. *Front Endocrinol (Lausanne).* 2021;12:667066. doi:10.3389/fendo.2021.667066
89. Chen H, Cao T, Zhang B, Cai H. The regulatory effects of second-generation antipsychotics on lipid metabolism: potential mechanisms mediated by the gut microbiota and therapeutic implications. *Front Pharmacol.* 2023;14:1097284. doi:10.3389/fphar.2023.1097284
90. Dias MF, Nogueira YJA, Romano-Silva MA, Marques de Miranda D. Effects of antipsychotics on the gastrointestinal microbiota: a systematic review. *Psychiatry Res.* 2024;336:115914. doi:10.1016/j.psychres.2024.115914
91. Misera A, Łoniewski I, Palma J, et al. Clinical significance of microbiota changes under the influence of psychotropic drugs. An updated narrative review. *Front Microbiol.* 2023;14:1125022. doi:10.3389/fmicb.2023.1125022
92. Biazzo M, Deidda G. Fecal microbiota transplantation as new therapeutic avenue for human diseases. *J Clin Med.* 2022;11(14):4119. doi:10.3390/jcm11144119
93. Cronin P, Joyce SA, O'Toole PW, O'Connor EM. Dietary fibre modulates the gut microbiota. *Nutrients.* 2021;13(5):1655. doi:10.3390/nu13051655
94. Gill SK, Rossi M, Bajka B, Whelan K. Dietary fibre in gastrointestinal health and disease. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):101-116. doi:10.1038/s41575-020-00375-4
95. Perrone P, D'Angelo S. Gut microbiota modulation through mediterranean diet foods: implications for human health. *Nutrients.* 2025;17(6):948. doi:10.3390/nu17060948
96. Singh TP, Natraj BH. Next-generation probiotics: a promising approach towards designing personalized medicine. *Crit Rev Microbiol.* 2021;47(4):479-498. doi:10.1080/1040841X.2021.1902940
97. Zandifar A, Badrfam R, Mohammaditabar M, et al. The effect of prebiotics and probiotics on levels of depression, anxiety, and cognitive function: a meta-analysis of randomized clinical trials. *Brain Behav.* 2025;15(3):e70401. doi:10.1002/brb3.70401
98. Strain R, Stanton C, Ross RP. Effect of diet on pathogen performance in the microbiome. *Microbiome Res Rep.* 2022;1(2):13. doi:10.20517/mrr.2021.10

99. Yadav MK, Kumari I, Singh B, Sharma KK, Tiwari SK. Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. *Appl Microbiol Biotechnol*. 2022;106(2):505-521. doi:10.1007/s00253-021-11646-8

100. Chua CK, Chia KH. A brief review of educational therapy and its current role: part 1. *Unlimited Human*. 2023;4-5. doi:10.5281/zenodo.15219971

101. Toader C, Dobrin N, Costea D, et al. Mind, mood and microbiota-gut-brain axis in psychiatric disorders. *Int J Mol Sci*. 2024;25(6):3340. doi:10.3390/ijms25063340

102. Sanada K, Montero-Marin J, Alda Díez M, et al. Effects of mindfulness-based interventions on salivary cortisol in healthy adults: a meta-analytical review. *Front Physiol*. 2016;7:471. doi:10.3389/fphys.2016.00471

103. Aguilar-Raab C, Stoffel M, Hernández C, et al. Effects of a mindfulness-based intervention on mindfulness, stress, salivary alpha-amylase and cortisol in everyday life. *Psychophysiology*. 2021;58(12):e13937. doi:10.1111/psyp.13937

104. Nesbitt AD. Delayed sleep-wake phase disorder. *J Thorac Dis*. 2018; 10(Suppl 1):S103-S111. doi:10.21037/jtd.2018.01.11

105. Sun SY, Chen GH. Treatment of circadian rhythm sleep-wake disorders. *Curr Neuropharmacol*. 2022;20(6):1022-1034. doi:10.2174/1570159X19666210907122933

106. Trompeter N, Bussey K, Forbes MK, Mitchison D. (2021). Emotion dysregulation within the CBT-E model of eating disorders: a narrative review. *Cognitive Therapy and Research. 2021;45*(6):1021-1036. doi:10.1007/s10608-021-10225-5

107. Malik K, Ibrahim M, Bernstein A, et al. Behavioral activation as an ‘active ingredient’ of interventions addressing depression and anxiety among young people: a systematic review and evidence synthesis. *BMC Psychol*. 2021;9(1):150. doi:10.1186/s40359-021-00655-x

108. Di Sante J, Akeson B, Gossack A, Knäuper B. Efficacy of ACT-based treatments for dysregulated eating behaviours: a systematic review and meta-analysis. *Appetite*. 2022;171:105929. doi:10.1016/j.appet.2022.105929

109. Chang C, Fraga J. How grief upsets your gut health. *Time*. 2022. Available: https://time.com/6193214/grief-gut-health/?utm_source=chatgpt.com

110. Khajuria A, Kumar A, Joshi D, Kumaran SS. Reducing stress with yoga: a systematic review based on multimodal biosignals. *Int J Yoga*. 2023; 16(3):156-170. doi:10.4103/ijoy.ijoy_218_23

111. van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. *Sleep Med Rev*. 2018;38:3-16. doi:10.1016/j.smrv.2017.02.001

112. BaHammam AS, Pirzada A. Timing matters: the interplay between early mealtime, circadian rhythms, gene expression, circadian hormones, and metabolism-a narrative review. *Clocks Sleep*. 2023;5(3):507-535. doi:10.3390/clockssleep5030034

113. Kosanovic Rajacic B, Sagud M, Pivac N, Begic D. Illuminating the way: the role of bright light therapy in the treatment of depression. *Expert Rev Neurother*. 2023;23(12):1157-1171. doi:10.1080/14737175.2023.2273396

114. Chunduri A, Reddy SDM, Jahanavi M, Reddy CN. Gut-brain axis, neurodegeneration and mental health: a personalized medicine perspective. *Indian J Microbiol*. 2022;62(4):505-515. doi:10.1007/s12088-022-01033-w

115. Williams, N. PHQ-9. *Occupational Medicine*. 2014;64(2):139-140. doi:10.1093/occmed/kqt154

116. Williams, N. (2014b). The GAD-7 questionnaire. *Occupational Medicine. 2014;64*(3):224. doi:10.1093/occmed/kqt161

117. Camilleri M. Fifty-point IBS-SSS responders but persistence of moderate severity IBS in over 40% of those on diet. *Gut*. 2022. doi:10.1136/gutjnl-2022-328211

118. Tripathi A, Das A, Kar SK. Biopsychosocial model in contemporary psychiatry: current validity and future prospects. *Indian J Psychol Med*. 2019;41(6):582-585. doi:10.4103/IJPSYM.IJPSYM_314_19

119. Chia KH, Tan MK, Loi CTT. Re-examining the controversial case of ‘autistic enterocolitis’: the role of gut-brain xis in autism spectrum disorder. *ISRG J Clin Med Medical Res*. 2025;2(3):1-11. doi:10.5281/zenodo.15335311

120. Grant AD, Erfe MCB, Delebecque CJ, et al. *Lactiplantibacillus plantarum* Lp815 decreases anxiety in people with mild to moderate anxiety: a direct-to-consumer, randomised, double-blind, placebo-controlled study. *Benef Microbes*. 2025;16(5):521-532. doi:10.1163/18762891-bja00073